

A Study to compare the analgesic effect of Intrathecal 0.5% hyperbaric Bupivacaine with Intrathecal 0.5% hyperbaric Bupivacaine plus Ketamine in patients presenting for Intracavitary High Dose Radiation(HDR) brachytherapy

By

Dr Justin Arun Kumar

A dissertation submitted in partial fulfillment of MD ANAESTHESIOLOGY examination conducted by Dr. M. G. R Medical University Tamil Nadu, Chennai to be held in March 2009



**DEPARTMENT OF ANAESTHESIOLOGY
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DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled “*Study to compare the analgesic effect of Intrathecal Hyperbaric Bupivacaine with Intrathecal Hyperbaric Bupivacaine plus Ketamine in patients presenting for Intracavitary High Dose Radiation (HDR) brachytherapy*” is a bonafide and genuine research work carried out by me under the guidance of **Dr Sarah Ninan** Professor, Head of the department of Anaesthesiology, CMC Vellore and **Dr Rebecca Jacob** Professor, Department of Anaesthesiology, CMC Vellore.

Date:

Place: Vellore.

Dr Justin Arun Kumar, DA

CERTIFICATE

This is to certify that this dissertation entitled ***“Study to compare the analgesic effect of Intrathecal Hyperbaric Bupivacaine with Intrathecal Hyperbaric Bupivacaine plus Ketamine in patients presenting for Intracavitary High Dose Radiation (HDR) brachytherapy”*** is a bonafide work done by ***Dr Justin Arun Kumar***, under my direct guidance and supervision as a Guide and Head of the department of Anaesthesiology, CMC Vellore in partial fulfillment for the requirement of MD Anaesthesiology examination conducted by Dr M.G.R Medical University, Chennai to be held in March 2009.

Date:

Place: Vellore

Dr Sarah Ninan,
Guide and HOD
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Acknowledgments

I must first thank GOD Almighty in whom I believe, whose presence and blessing was present throughout the course of my study and for making the people around me to be so wonderful, cooperative and helpful for the successful completion of this study.

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November 13, 2008

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Sub: FLUID Research grant project NEW PROPOSAL:
Prospective Randomized Controlled Study to compare the analgesic effect of plain
Intrathecal Bupivacaine and Intrathecal Bupivacaine plus Ketamine in patients presenting
for Intracavitary High Dose Rate (HDR) brachytherapy.
Dr. Justin Arun Kumar, PG Registrar, Anaesthesia, Dr. Rebecca Jacob, Anaesthesia.

Ref: 1) R.C. Min. No. 6576 dated 11.06.2008.
2) IRB Min. No. IRB(EC)-22-11-06-2008.

Dear Dr. Justin Arun Kumar,

The Institutional Review Board (Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Prospective Randomized Controlled Study to compare the analgesic effect of plain Intrathecal Bupivacaine and Intrathecal Bupivacaine plus Ketamine in patients presenting for Intracavitary High Dose Rate (HDR) brachytherapy" on June 11, 2008.

The Committees reviewed the following documents:

1. Format for application to IRB submission.
2. Information Sheet (English, Hindi, Bengali, Tamil).
3. Informed Consent Form (English, Hindi, Bengali, Tamil).
4. A CD containing documents 1-3.

The following Ethics Committee members were present at the meeting held on June 11, 2008 at 10:00 am in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. George Thomas	MBBS, D.Ortho	Chairperson (IRB) & Orthopaedic Surgeon, St. Isabel Hospital, Chennai & Editor, Indian Journal of Medical	Non-CMC Staff.



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Mr. Malia Joshva (on behalf of Rev. Dr. T. Arul Dhas)	M.Sc., BD, Ph.D.	Chaplain, CMC	
Mr. Harikrishnan	BL.	Lawyer	Non-CMC staff.
Dr. Sujith Chandy	MBBS, MD	Professor, Pharmacology Dept. CMC.	
Mrs. Sheeba Chandy (on behalf of Mrs. Bharthy Jacob)	M.Sc. (Nursing)	Dean, College of Nursing	
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Dr. Varghese Cherian	MBBS, DA, MD.	Professor, Anaesthesia Dept. CMC.	
Mrs. S. Pattabhiraman	BSc, DSSA	Social Worker, Vellore	Non-CMC-Staff
Dr. Gagandeep Kang	MD, PhD, FRCPATH.	Dy. Chairperson (IRB), Professor of Microbiology & Addl. Vice Principal (Research), CMC.	

We approve the project to be conducted in its presented form.

The Institutional Ethics Committee / Independent Ethics Committee expects to be informed about the progress of the project, any SAE occurring in the course of the project, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

A sum of Rs. 3,500/- (Rupees three thousand five hundred only) is sanctioned for 3 months and out of which a maximum of Rs 1500/- can be spent for stationery, printing, Xeroxing and computer charges (if computers used are within the institution).

Yours sincerely,

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INTRODUCTION

The choice of treatment for cervical cancer in its early stages is surgery. Radiation or chemo-radiation therapies are reserved for high-risk patients in their early stages or in those who have advanced disease. Radiation therapy is delivered initially by external beams using high energy photons or gamma rays which is followed by internal radiation known as brachytherapy.

Brachytherapy is given in two forms, one as high dose radiation (HDR) and other as low dose radiation (LDR). In both HDR and LDR, applicators are placed in the uterus or vagina. Later, radiation is given and the applicators are removed about 4-5 hrs or 24-36 hrs after HDR or LDR respectively. The period till the applicators are removed is painful and uncomfortable. Hence relief of pain during this period prevents adverse psychological effects in these patients who have already been stressed with a diagnosis of malignancy.

Providing anaesthesia to patients coming for insertion of vaginal applicators for intracavitary high dose brachytherapy involves a higher risk as compared to other patients. They could have comorbid factors like advanced age, hypertension, diabetes, ischemic heart disease, anaemia etc. and hence are more prone for perioperative complications. The other factor is that, they require analgesia and immobilization till the brachytherapy is completed.

This procedure could be performed under general anaesthesia or under a regional technique like a subarachnoid or epidural block. In our set up these patients receive HDR and get discharged on the same day and the next fraction is given the following week. General anaesthesia does not provide the required analgesia and immobilization till the applicators are removed and could be associated with postoperative nausea and vomiting. As compared to

general anaesthesia, epidural or spinal anaesthesia is safe and practical. Epidural anaesthesia through an indwelling catheter can provide adequate analgesia and immobilization but it is not cost effective as these patients get discharged on the same evening.

Subarachnoid block is a safe, simple, rapid onset and cost effective regional anaesthetic technique as compared to other forms of anaesthesia. Blocking the transmission of nociception at the level of the spinal cord has been the main target of study in both acute and chronic pain states and various adjuvants are being used to extend the analgesic effect of local anaesthetics .

Spinal adjuvant drugs like opioids (fentanyl, morphine), ketamine, clonidine, neostigmine, adrenaline and adenosine are being used. Opioids can cause respiratory depression, postoperative nausea and vomiting and urinary retention. Clonidine can cause bradycardia, hypotension and sedation while neostigmine can cause nausea and vomiting. Adenosine and adrenaline do not prolong the duration of analgesia like the other drugs.

Ketamine is a popular anaesthetic and analgesic and it does not cause any of the side effects mentioned above which is more important in this group of patients. Studies have shown that preservative free ketamine as a spinal anaesthetic adjuvant along with 0.5% hyperbaric bupivacaine can provide adequate analgesia and immobilization during the insertion of the applicators and till the completion of radiation therapy.

This prospective double blinded randomized crossover study was designed to assess the duration of analgesia and to study the effects of addition of ketamine to hyperbaric bupivacaine given intrathecally in patients coming for intracavitary brachytherapy.

AIM

“To study the duration of analgesia and safety profile of intrathecal hyperbaric bupivacaine with ketamine in patients coming for placement of vaginal applicators for high dose radiation intracavitary brachytherapy”.

OBJECTIVES

1. Duration of analgesia.
2. Duration of sensory and motor block.
3. Incidence of side effects.

REVIEW OF LITERATURE

The literature has been reviewed under the following headings.

1. Pain and its implications.
2. Spinal anaesthesia.
3. Spinal analgesia.
4. Ketamine
5. Clinical studies on intrathecal / epidural/ caudal ketamine.

1. Pain and its implications:

International association for the study of pain (IASP)¹ defines pain as **“an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”**.

Acute pain in the perioperative setting has been defined as “pain that is present in a surgical patient because of preexisting disease, the surgical procedure (e.g. associated drains, chest or nasogastric tubes, complications), or a combination of disease related and procedure related sources”. (ASA task force on pain management -acute pain section)²

Acute postoperative pain is a complex reaction to tissue injury, visceral distention or disease. It is a manifestation of anatomical and physiological responses that result in an

unpleasant sensory and emotional experience.

Pathophysiological consequences of pain³

1. Cardiovascular system - tachycardia, hypertension, increased systemic vascular resistance and increased cardiac work.
2. Pulmonary system - hypoxia, hypercarbia, atelectasis, decreased cough vital capacity and functional residual capacity, and ventilation perfusion mismatch.
3. Gastrointestinal tract - nausea, vomiting and ileus.
4. Renal - oliguria and urinary retention.
5. Extremities - skeletal muscle pain and restriction of mobility.
6. Endocrine - vagal inhibition, increased adrenergic activity, metabolism and oxygen consumption.
7. CNS - anxiety, fear, sedation and fatigue.
8. Immunological - impairment.

Rationale of postoperative pain relief

The aim of postoperative analgesia is to provide subjective comfort and to inhibit trauma induced nociceptive impulses. This is in order to blunt the autonomic and somatic reflex responses to pain and subsequently to enhance restoration of function by allowing the patients to breathe, cough and ambulate early.

Pain control may have a further benefit of improving clinical outcome by reducing

the incidence of postoperative complications such as myocardial infarction or ischemia, impaired wound healing, atelectasis, thrombo-embolic events, peripheral vasoconstriction and metabolic acidosis.

Effect of post operative analgesia on surgical outcome⁴

Optimal (dynamic) pain relief is a prerequisite for an early postoperative recovery. A reduction in the surgical stress response (endocrine, metabolic and inflammatory) will decrease the incidence of postoperative organ dysfunction and lead to an improved outcome.

Pharmacological Management ⁵

During recent years, there has been a tremendous increase in our understanding of the physiology of acute pain, development of new analgesics and techniques of administration. Various routes which are available for post operative analgesia include intramuscular, subcutaneous, intravenous, oral, rectal, transdermal, epidural, intrathecal, caudal etc.

Spinal anaesthesia

History

The first spinal anaesthesia though inadvertently, was produced by Leonard Corning a neurologist in New York (1855 – 1923), while he was experimenting with cocaine on the spinal nerves in dog and accidentally pierced the duramater. His next patient was a man with

seminal incontinence who developed transient paralysis of the lower limbs after the spinal injection. He coined the term 'Spinal anaesthesia'. Deliberate Lumbar puncture was produced by Heinrich Irenaeus Quincke (1842 – 1922) who was aware of the anatomy of the spinal cord.

The first planned spinal anaesthesia for surgery in man was administered by Augustus Karl Gustav Bier (1861-1949) on 16th August 1898, in Kiel. A surgeon by profession, he injected 3 ml of 0.5% cocaine solution into a 34 year old labourer. He also experimented on himself with the help of his assistant Hildebrandt. Smith and Porter reported in 1915 that the fall in blood pressure after the spinal anaesthetic is due to the paralysis of the vasomotor fibres in the splanchnic area and the importance of hyperbaricity. The midline approach was demonstrated by Arthur E Barker and the saddle block was demonstrated by Adriani and Roman - Vega.⁶

Definition

Spinal anaesthesia consists of temporary interruption of the neural transmission within the subarachnoid space produced by an injection of anaesthetic solution into the cerebrospinal fluid.

Anatomy

Vertebral column consists of 33 vertebrae and 31 pairs of spinal nerves. The spinal cord ends at the level of the lower border of L1 vertebra. The structures traversed by the needle while performing spinal anaesthesia are skin, subcutaneous tissue, supraspinous ligaments, interspinous ligaments, ligamentum flavum, epidural space, duramater, subdural

space, arachnoid mater and the subarachnoid space where the drug is placed. The pia mater and spinal cord proper are beneath this space. The contents of the subarachnoid space are cerebrospinal fluid, spinal nerves, dentate ligaments (a spongy reticulum of fibres connecting the pia mater to the arachnoid mater), arteries, veins and lymphatics.

The spinal cord is supplied by three longitudinal arteries, a single anterior spinal artery which runs in the anterior commissural fissure which supplies the anterior two thirds of the spinal cord. There are two posterior spinal arteries which supply the posterior third of the cord. There are radicular arteries which contribute to the anterior and posterior spinal arteries. The most important is the anterior radicular artery, called the artery of Adamkiewicz.

Venous drainage is similar to the arterial blood supply. There are three anterior and three posterior veins which drain into the vertebral veins, ascending lumbar veins and the azygos veins.

Cerebrospinal fluid (CSF)

Cerebrospinal fluid was first discovered by Dominico Cotugno in 1764. Its circulation was described by F. Magendie in 1825, who christened it as the cerebrospinal fluid⁷. It is an ultra filtrate of plasma with which it is in hydrostatic and osmotic equilibrium. It is secreted from the choroids plexus at the rate of 0.3 – 0.4 ml / minute. The total volume is about 120 - 150 ml of which 25 – 35 ml is in the spinal subarachnoid space. In the horizontal position the CSF pressure ranges from 60 – 80 mmHg.

Physical properties

pH: 7.4

Specific gravity: 1.0069

Proteins: 20mg%

Glucose: 45 – 80 mg%

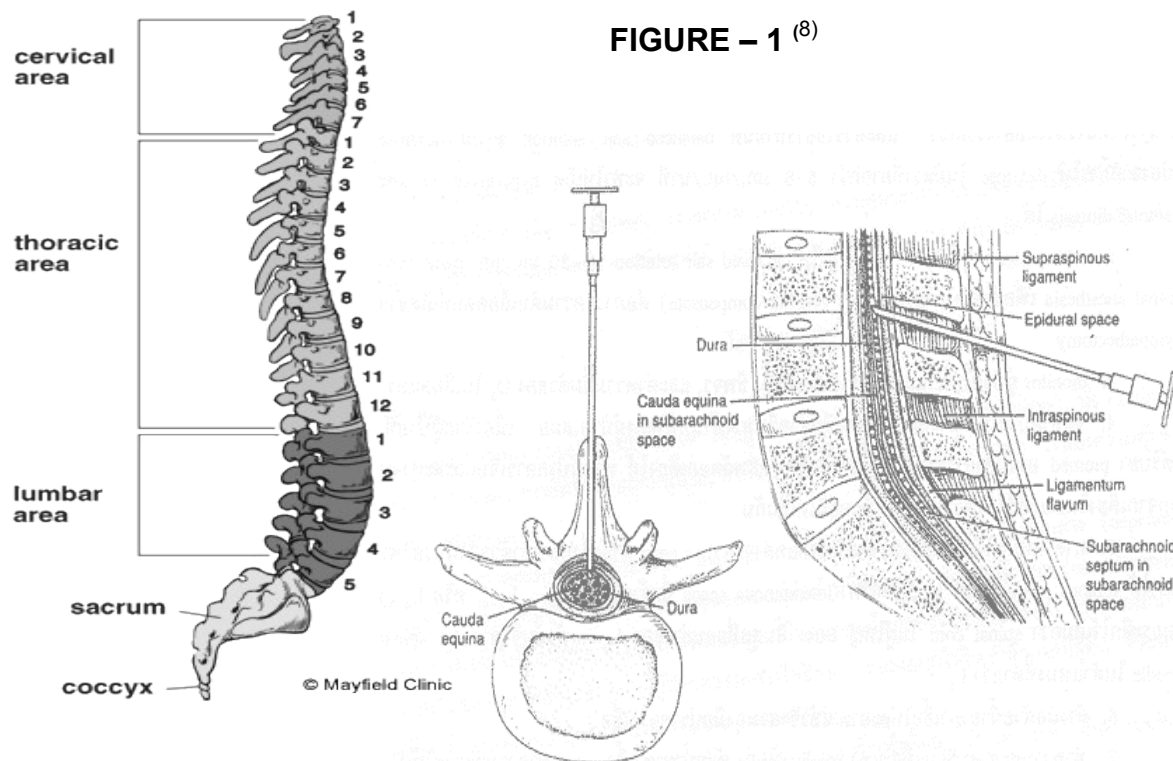
Density: 1.0003

Baricity: 1.000

Functions:

- It serves to support and cushion the brain against trauma.
- It removes waste products of metabolism, drugs and other substances that diffuse into the brain from the blood.
- It has an important role in integrating the brain and peripheral endocrine functions.
- The changes in the ionic concentration of calcium, potassium and magnesium in the CSF may affect the blood pressure, heart rate, vasomotor reflexes, respiration, muscle tone and emotional state.

spinal column



FIGU

RE – 2⁽⁹⁾

Spinal analgesia

The pharmacology of pain perceived in the spinal cord is complex and almost all the receptors found in the CNS are also found in the spinal cord ⁽¹⁰⁾. At the periphery most of the

thermal and mechanical nociceptive signals arise from the activation of polymodal nociceptors which are innervated by A α and C fibres. The mediators are cytokines, nerve growth factors, catecholamines, bradykinin, 5-hydroxy tryptamine and prostanoids.

There is considerable evidence for the involvement of excitatory amino acids glutamate, aspartate and a number of peptides in the nociceptive transmission of pain. They include the tachykinin family of peptides, calcitonin gene related peptide (CGRP), somatostatin, vasoactive intestinal peptide, galanin, bombesin and neurotensin.

The dorsal horn of the spinal cord is the site of termination of the primary afferent nociceptive neurons. They end primarily on laminae I, II, and V, where they interact with various second order neurons. There are two different classes of secondary neurons, the first class is known as the “nociceptive specific” or “high threshold” neurons and the second class is known as the “wide dynamic range” (WDR) or “convergent” neurons. Nociceptive specific neurons are responsive to noxious stimuli and are placed superficially in the dorsal horn. But the WDR do not respond to non-noxious stimuli; however they become sensitized and hyper responsive by a phenomenon called the “Wind Up”, where even a tactile stimulus will result in hyperalgesia.⁽⁶⁾

These excitatory amino acids act on the NMDA and the non-NMDA receptors and the latter group consists of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), metabotropic and kainite. Antagonists against these receptors have gained importance in the research on analgesia. There are other receptors involved in the nociceptive transmission or modulation and they include the opioid (μ , δ and K), the α -adrenergic, the gamma-amino-butyric acid (GABA), the serotonin (5HT) and the adenosine receptors.

Modulation of pain

Transmission of pain from periphery is subjected to modulation at various levels of the neuraxis. They are inhibited by the local interneurons or the descending pathways. Modulation at the dorsal horn is by both exogenous and endogenous agents which act on the opioid (μ , δ and K), the α -adrenergic, the gamma-amino-butyric acid (GABA), and the glycine receptors.

Receptors:

- Opioid receptors
- N-methyl d-aspartate (NMDA) receptors
- Serotonergic receptors
- α -2 adrenergic receptors
- Cholecystokinin (CCK) receptors
- Gamma amino butyric acid (GABA) receptors.

1) Opioid receptors :

Opioid receptors form a major spinal inhibitory system in the pain pathway.

Opioids act by activating three opioid receptors; the μ (μ), δ (δ), and κ (K). The highest level of opioid receptors in the spinal cord are found around the C-fiber terminal zones in lamina 1 and the lamina 2 (substantia gelatinosa) with lower concentrations in the deeper layers. Lamina 1 and 5 are known to respond principally to noxious stimuli, a partial explanation for the analgesic effects of ketamine may be a

lamina specific suppression of neuronal activity. The endogenous opioid peptides namely the enkephalins, dynorphins and endorphins are the natural ligands for these receptors which are not entirely specific but a number of other synthetic agents with high selectivity are available for study of these receptors. Opioid peptides synthesis can be altered in animal models in different pain states. For example, dynorphin levels in the spinal cord during inflammation are increased enormously due to the switching of the gene for the synthesis of the parent peptide. The peptidase inhibitors can protect the breakdown of these peptides and can be used to function as opioids and their receptors.

2) N-methyl d-aspartate (NMDA) receptors:

NMDA receptors belong to the glutamate group of receptors. It is present on the post synaptic neurons in the dorsal horn. It is activated by the excitatory amino acids like glutamate released from the primary neurons in response to noxious stimulus. NMDA receptors are implicated in many ways in the spinal mechanism of pain and more so in chronic pain states. It is involved in central hyperalgesia and wind up phenomenon. A recent clinical study done on disordered central processing in sympathetic dystrophy drive showed that local anaesthetics abolished all symptoms. This system requires a peripheral afferent input in the spinal cord which is then amplified and prolonged by a central process with the NMDA receptor playing a key role. NMDA receptors are also blocked by high concentrations of opioids³⁹. Ketamine is a NMDA receptor antagonist.

3) Serotoninerbic receptors:

There are a significant number of serotonergic receptors in the spinal cord and administration of serotonin on the spinal cord inhibits the nociceptive neuronal output. Ketamine prevents neuronal uptake of monoamines – serotonin and nor adrenaline and increases their concentration at the spinal and the supraspinal levels. The increased levels of these monoamines may be responsible for the spinally mediated action of ketamine. Antagonists of these monoamines, namely methysergide and phentolamine have been proved to antagonize the analgesic effect of ketamine.

4) α -2 adrenergic receptors:

The descending noradrenergic system from the brain and the midbrain also control nociception and can be manipulated by the opioids.

Descending pathways

This concept was developed by Melzack and Wall with the proposal of “the gate theory”. These pathways arise from many supraspinal structures including the hypothalamus, periaqueductal grey matter and nucleus raphe magnus. They involve the action of endogenous opioids, serotonin and GABA. Elucidation of inhibitory pathways is one of the modalities of pain control e.g. TENS, deep brain stimulation, epidural and spinal cord stimulation.

Ascending pathways:

Spinal structures involve the spinothalamic, the spinoreticular, and the spinomesencephalic tracts which ascend in the contralateral side of the cord. Acute pain

could be treated by cordotomy, extralemniscal myelotomy and commissural myelotomy.

Supraspinal structures The station for the second order neurons is the thalamus. Two nuclei are involved i) ventro-posterior and ii) medial nuclei and these serve different functions.

Cortical structures involve two areas i) serving as sensory discriminative component in the somatosensory cortex and ii) affecting pain perception in the cingulated cortex.

Ketamine

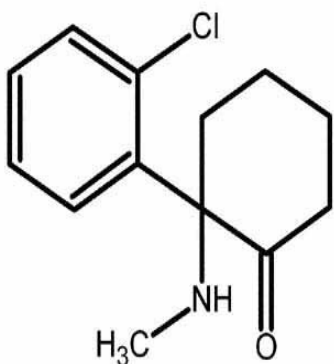
Ketamine an anaesthetic and analgesic drug, being a phencyclidine derivative is used extensively.

History:

In 1958, phencyclidines (phenyl cyclohexyl piperidine) were introduced in clinical anaesthesia but due to its unacceptable effects like hallucinations, confusion and delirium the usage was stopped. In 1959, cyclohexamine was tried which had more side effects than phencyclidines and had no analgesic effect.

In 1962 ketamine was synthesized by Stevens and is one of the 200 phencyclidine derivatives. It was tried on humans in 1965 and was officially released for clinical use in 1970. In 1999 it became a schedule III substance under CSA.

Chemistry:



Ketamine is chemically a 2-(o-chlorophenyl)--(methylamino) cyclohexane (hydrochloride) compound. Ketamine has a chiral center and presently marketed as a racemic mixture of its two enantiomers S (+) ketamine and R (-) ketamine in NaCl solution with a pH of 3.5 to 5.5. It is prepared in three concentrations of 10, 50 and 100 mg/ml with benzethonium chloride as a preservative. Ketamine has a molecular weight of 238, is partially water soluble at a pH of 7.4 (pKa –7.5) and 5 - 10 times

more lipid soluble than thiopental.

Pharmacokinetics:

Its pharmacokinetics can be explained by a two compartment model. Its $t_{1/2}$ distribution phase is 11 -16 minutes and being very lipid soluble its V_d is 3L/kg. The clearance of the drug is 12 -17 ml/kg/min and $t_{1/2}$ elimination is 2 -3 hours. The plasma level of ketamine for hypnosis and amnesia during surgery is approximately 0.7 to 2.2 mcg/ml and awakening occurs at a level below 0.5mcg/ml.

Metabolism:

Ketamine is metabolized extensively by the hepatic microsomal enzymes, the main pathway being demethylation of ketamine by cytochrome P-450 enzyme to norketamine. This gets hydroxylated and conjugated to form inactive water soluble glucoronide metabolites which are excreted by the kidneys. Less than 4% of the drug gets excreted unchanged in urine and less than 5% in faeces.

Isomers :

There are two optical isomers of ketamine due to the presence of an asymmetrical carbon atom. These are the positive (S) isomer and the negative (R) isomer. S-isomer as compared to R-isomer causes i) intense analgesia ii) rapid metabolism and recovery and iii) a lower incidence of emergence reactions. This suggests that they have different sites of action and receptors¹¹.

Pharmacodynamics:

Central nervous system:

It causes dissociative anaesthesia which is a cataleptic state with profound analgesia, open eyes and intact corneal, cough and swallow reflexes due to thalamo-cortical dissociation. Amnesia is also present but may not be as profound as that seen with the benzodiazepines. The onset of action is less than 30 seconds. There is pupillary dilatation, nystagmus, lacrimation, salivation, an increase in the muscle tone and purposeless but coordinated movements of the limbs. There is a good correlation between the blood concentration and CNS effects which is about 0.6–2 mcg/ml for adults and 0.8–4mcg/ml in children and awakening occurs in 15- 30 minutes.

With the S-enantiomer a slightly lower dose is adequate and due to a 10% increase in hepatic biotransformation as compared to the R- enantiomer a faster recovery is seen. Analgesia occurs at a plasma concentration of approximately 0.1mcg/ml. Its main action is cerebral functional disorganization causing thalamocortical dissociation and an increase in the function of the limbic system.

Though controversial it is shown that it can be used in neurologically impaired patients as it does not increase the intracranial pressure and does not cause seizure activity but it increases cerebral metabolism and C_{mro2} .

Cardio vascular system:

Ketamine is a known sympathomimetic and it increases the blood pressure and heart rate. It acts on the postsynaptic NMDA receptors and the presynaptic afferent processes in

the medial nucleus tractus solitarius. The C-type afferents which mediate powerful arterial baroreflexes effects are also affected¹². Ketamine is also known to have an effect on the parasympathetic cardiac vagal efferent activity through which it causes an increase in the heart rate and produces sinus arrhythmia¹³.

Respiratory system :

Ketamine is a respiratory stimulant and causes bronchodilatation due to a NMDA receptor independent action by interfering with Ca^{++} required for bronchoconstriction due to histamine release¹⁴. It rarely causes respiratory arrest but increased salivation and retention of airway reflexes like cough, gag, sneeze and swallow not adequate for airway safety are seen.

Gastro-intestinal:

Peripherally administered ketamine reduces both VMR and motility reflexes, but not at doses used in the anaesthetic mixtures (1.8-2.4 mg kg h⁻¹). Effect on the motility reflexes is likely to be due to a non-NMDA receptor action, possibly on the nicotinic receptors¹⁵.

Other effects:

- It suppresses the neutrophil production of inflammatory mediators thereby improving the blood flow.
- It reduces the migration of leukocytes through endothelial cells.
- It suppresses the proinflammatory cytokine production in blood.
- It inhibits the activity of hepatic microsomal enzymes, CYP2D1 and CYP3A by 10-20%.

Mechanism of action:

Ketamine is a NMDA blocker with a complicated mechanism of action. It is used both as an anaesthetic and analgesic. It acts on many receptors mainly the NMDA and the others are the opioid, the serotonin and the muscarinic receptors.

Orser and Beverley A. MD, in their study showed that ketamine inhibits the NMDA receptor by two distinct mechanisms (1) it blocks the open channel and thereby reduces mean channel open time and (2) it decreases the frequency of channel opening by an allosteric mechanism¹⁶.

Colin J. L. McCartney et al, in their study showed that the mechanism of ketamine and dextromethorphan causing preventive analgesia is through inhibition of central sensitization and thereby causing a partial opioid tolerance¹⁷.

Kawamata and Tomoyuki M.D in their study showed that ketamine produced antinociceptive effects through the activation of the monoaminergic descending inhibitory system, whereas in a unilateral peripheral inflammation induced hyperalgesic state, the monoaminergic system did not contribute to the antihyperalgesic effect of ketamine. The mechanisms of antinociceptive and antihyperalgesic properties of ketamine are different¹⁸.

Finck.A.Donald M.D. suggested that ketamine induced analgesia is also mediated by the opioid receptors as the analgesic effect of ketamine can be antagonized by naloxone¹⁹.

At cellular level ketamine blocks the Na^+ and the K_{DR} channels in the superficial dorsal horn neurons of the lumbar spinal cord at clinically relevant concentrations after local and intrathecal administration. Ketamine reduces the excitability of the neurons which may play an important role in the complex mechanism of action during spinal anaesthesia²⁰.

Uses:

- a) Induction and maintenance of general anaesthesia in ASA IV (or V) patients with respiratory or cardiovascular disease (other than CAD), especially reactive airway disease or hemodynamic compromise due to hypovolemia or intrinsic myocardial disease (other than CAD).
- b) Reactive airway disease, asthma
- c) Rapid-sequence induction in otherwise healthy polytrauma victims following massive hemorrhage
- d) Patients in septic shock
- e) Cardiac tamponade and constrictive pericarditis (ketamine maintains heart rate and filling pressure)
- f) Congenital heart disease, especially with a propensity for R to L shunt
- g) Malignant hyperthermia susceptible patients with a large anterior mediastinal mass when spontaneous ventilation is required during induction and intubation
- h) Cardiac anaesthesia for correction of valvular or ischemic heart disease: ketamine and diazepam or midazolam (with sufentanil) by a continuous infusion because it

causes

- minimal hemodynamic perturbations
- profound analgesia
- dependable amnesia
- uneventful convalescence

i) Continuous infusion of ketamine and propofol for total intravenous anaesthesia (TIVA) causes profound analgesia without abolishing spontaneous ventilation.

Sedation and Analgesia:

- 1) Preoperative sedation/analgesia
- 2) Sedation (especially paediatric) for procedures in remote locations
 - Cardiac catheterization
 - Radiation treatment
 - Radiologic studies
 - Change of dressing (e.g. post burn injury)
 - Dental procedures
- 3) During primary propofol sedation/anaesthesia with spontaneous ventilation, ketamine boluses provide good analgesia (without respiratory depression) during injection of local anaesthetics.
- 4) As a supplement to regional anaesthesia, prior to or after the block
- 5) Postoperative analgesia

Other uses:

- 1) Treatment of status asthmaticus.
- 2) Inhibition of reflex hypertensive response to urinary bladder distension (rats)³⁸.
- 3) Treatment of restless leg syndrome (ketamine 30-40 mg PO BID)
- 4) It has been suggested that ketamine may be used as an adjunct for psychotherapy in the treatment of heroin addiction.

Doses and routes of administration:

Ketamine can be administered by the intravenous, intramuscular, oral, rectal, nasal, epidural and intrathecal spaces.

General anaesthesia:

- 1) Intravenous Induction 0.5 - 2 mg/kg - the peak effect is in 30-60 seconds

Maintenance 0.5 - 1 mg/kg IV prn or 20 - 90 mcg/kg/min iv infusion.

- 2) For TIVA - continuous iv infusion of propofol and ketamine in a ratio of (4:1) (e.g. propofol 200 mg + ketamine 50 mg) the dose has to be reduced in elderly patients.

- 3) Intramuscular induction 4 - 10 mg/kg – the onset of action is 5 minutes and the peak effect is in 20 minutes

4) Sedation/analgesia

Route	Dose
IV	0.2 - 0.8 mg/kg
IM	2 - 4 mg/kg

IV infusion	5 - 10 mcg/kg/min
-------------	-------------------

5) Paediatrics

Route	Dose (mg/kg)
Oral	6 - 10
Nasal	6 - 10
IM	3 – 10
IV	0.5 – 2
Rectal	10

6) Intrathecal: 0.25 – 0.5 mg / kg

7) Epidural / Caudal: 0.5 mg /kg

Bioavailability

Route	% bioavailability
Nasal	50
Oral	20
IM	90

Emergence Delirium: Emergence from ketamine anaesthesia in the post operative period may be associated with visual, auditory, proprioceptive, and confusional illusions and delirium. Cortical blindness may be present. Patient can also have dreams and hallucinations during the first 24hrs which usually disappears within few hours.

The mechanism is due the depression of inferior colliculus and medial geniculate body. The incidence may range from 5% - 30% with an increased frequency seen in patients a) age >15 yrs b) females c) when the dose is more than 2mg/kg of ketamine and d) a history of personality problems. (White et al 1982)

Preventive measures include use of benzodiazepines with midazolam being more effective than diazepam. Thiopentone and dexmedetomidine can also be used to treat emergence delirium¹¹.

Relative contraindications:

- Patient with intracranial mass and elevated ICP
- Open eye injury (or whenever increased intraocular pressure would be harmful)
- As a sole anaesthetic agent in ischemic heart disease
- Patients with aneurysm
- Psychotic disease

Safety of Intrathecal ketamine

Intravenous ketamine has shown to have few neurotoxicity effects which were attributed to the preservative benzethonium chloride or chlorobutanol. When given

intravenously it was shown to cause brain cell death in perinatal rhesus monkey²¹. There were three cases of blindness reported by Fine Joseph et al after the use of ketamine²².

Even preservative free Intrathecal ketamine was found to produce histopathological changes suggesting neuronal injury in rabbits, but this was seen on repeated intrathecal injections and was also dependent on the dose of the drug⁴⁰. It was shown by Brock et al that intrathecal ketamine does not cause any macroscopic change but microscopically has caused edema of the nerve roots²³. Borgbjerg confirmed the lack of neurotoxicity on light and electron microscopy²⁴.

Ketamine - Dreams and realities²⁵

Ketamine though used mainly as an anaesthetic, can cause vivid dreams and hence it is used as a party drug. The other street names are Super K, Kitkat, Ecstasy, Green K, Purple, Special la coke, Jet, Honey oil and Super acid. It is illegal to possess ketamine without a license or a prescription in the USA. In India it is still available as an on the counter drug and is slowly becoming popular as a party drug. It is also known to give a “near death experience”. Ketamine as a drug of abuse can be mixed in beverages, smoked, and injected intramuscularly.

Clinical studies on Intrathecal / Epidural/ Caudal Ketamine.

Yatindra Kumar Batra et al conducted a study to determine whether ketamine alone or in combination with bupivacaine provided superior pain relief after surgery in patients undergoing knee arthroscopy. He observed that intraarticular bupivacaine with ketamine provided better pain relief than plain in day care arthroscopic knee surgery²⁶.

Togal T et al studied conducted a study to evaluate the effects of intrathecal S (+) ketamine added to a small dose of spinal bupivacaine in elderly patients undergoing transurethral prostate surgery. He concluded that Intrathecal S(+) ketamine administered with a small dose of bupivacaine provided a shorter onset time of motor and sensory block, a shorter duration of action and a lesser motor blockade in elderly males²⁷.

Vranken J H et al reported about a patient with severe neuropathic cancer pain who was successfully treated by continuous intrathecal infusion of morphine, bupivacaine, clonidine and S (+)-ketamine. The quality of life before and three weeks after the onset of spinal treatment revealed an improvement in pain relief. No clinical sign of neurologic deficit was observed during the spinal treatment with S (+)-ketamine. However, continuous intrathecal administration of S (+)-ketamine should be considered as the last modality of analgesia as there is no preclinical safety data on the use of intrathecal S (+)-ketamine²⁸.

Bion et al studied the effect of intrathecal ketamine for surgeries in war casualties. He observed that the dose of ketamine to produce clinical anaesthesia was 1-2 mg/kg and the duration of analgesia was 40-45 minutes which was devoid of respiratory and cardiac depression. The degree of sedation was more when a higher dose was used²⁹.

Bhattacharya D studied 100 patients belonging to ASA I and II grades scheduled for lower abdomen and lower extremity surgery under spinal anaesthesia who were divided into two groups of 50 patients each. The first group received 0.5% hyperbaric bupivacaine while the second group received a solution containing 2 ml of ketamine (100 mg), 2 ml of 5% dextrose and 1 ml of 1 in 10,000 adrenaline (0.1 mg). From the study, it was concluded that intrathecal ketamine with 0.5% bupivacaine as compared to plain 0.5% bupivacaine had significant clinical properties like shorter onset of sensory and motor block, shorter duration of sensory block, an almost equal duration of motor block, minimal changes in systolic blood pressure and pulse rate and a longer duration of postoperative analgesia. The intensity of analgesia, gradation of motor paralysis and central effects (sedation) in the ketamine with hyperbaric bupivacaine group was more than in the plain hyperbaric bupivacaine group³⁰.

Benrath J et al reported a patient with urethral carcinoma who had chronic neuropathic pain and was treated successfully with intrathecal administration of S (+)-ketamine and morphine. Plasma concentration of S (+)-ketamine was measured regularly throughout the treatment and continuous administration of S (+)-ketamine over a period of 3 months demonstrated a low plasma level and no unwanted side effects³¹.

Bansal et al used intrathecal ketamine in three doses of 50, 75, and 100 mg with and without adrenaline for emergency surgeries on lower limbs and lower abdomen. They found

that the sensory block was adequate in all the cases and observed motor block with higher doses of ketamine. There was no respiratory or cardiovascular depression and the duration of analgesia lasted for about 1-3 hours³².

Khubchand used ketamine 50mg intrathecally for a case of ruptured uterus and it provided satisfactory analgesia for the surgery without untoward cardiovascular or respiratory complications³³. Sekaran et al administered autoclaved preservative free ketamine intrathecally in a known asthmatic and found spinal ketamine as an effective and efficient mode of anaesthesia⁴².

Yanli Y et al conducted a randomized, double blinded study on 30 patients comparing two regimens for extradural anaesthesia - 20 ml of 0.5% bupivacaine, 25 mg of ketamine and 1 in 200 000 adrenaline with 20 ml of 0.5% bupivacaine, 0.5 ml of 0.9% saline and 1 in 200 000 adrenaline. The main outcome measures were onset time for acceptable bilateral anaesthesia and duration of postoperative analgesia. The time of onset of anaesthesia was reduced by 8 minutes in the bupivacaine-ketamine group as compared to the bupivacaine-saline group. In addition, the anaesthetic level was two segments higher in the bupivacaine-ketamine group (T7 versus T9) and side effects were similar in both the groups with no significant difference in the postoperative analgesic requirements between the groups. The addition of ketamine to bupivacaine given epidurally appears to be useful to reduce the onset time of blockade³⁴.

Punjabi N et al studied sixty paediatric patients aged 6 months to 10 years who underwent inguinal herniotomy and they were randomly allocated to receive 1 of the 3 solutions for a caudal epidural block. Group 1 received 0.75 ml/kg of 0.25% bupivacaine with

0.25 mg/kg of preservative-free ketamine, group 2 received 0.75 mL/kg of 0.25% bupivacaine with 0.5 mg/kg of ketamine, and group 3 received 0.75 mL/kg of 0.25% bupivacaine with 1 mg/kg of ketamine. They concluded that the mean duration of caudal analgesia was 8.8 hours in group 1 as compared to 22.1 hours in group 2 and 25.2 hours in group 3. Supplemental analgesic requirements with pethidine was significantly less in group 2 (4 subjects) and group 3 (no subject) as compared to group 1 (18 subjects). There was no difference in the incidence of motor blockade, urinary retention, emesis or sedation between the groups. Group 3 had a significantly higher incidence of side effects such as odd behavior, agitation and restlessness than groups 1 and 2. Thus they concluded in their study that the optimal dose of ketamine was 0.5 mg/kg added to 0.75 mL/kg of 0.25% bupivacaine for caudal epidural block without an increase in the incidence of side effects³⁵.

Kathirvel S et al studied the effect of bupivacaine with and without ketamine in patients who underwent intracavitary brachytherapy. He found that the onset time of sensory and motor block and the duration of spinal analgesia were comparable between the groups. The duration of motor blockade was shorter and requirement for intravenous fluids in the perioperative period was lesser in the ketamine group. Significantly, more patients in the ketamine group had adverse events like sedation, dizziness, nystagmus, strange feelings and postoperative nausea and vomiting. It was concluded that although the addition of ketamine to spinal bupivacaine had a local anaesthetic additive effect, it did not provide postoperative analgesia and the central adverse effects of ketamine limited its spinal use³⁶.

MATERIAL AND METHODS

Study area: Christian Medical College & Hospital, Vellore, known as "*CMC Vellore*", was founded by Dr. Ida S. Scudder and is located in the city of Vellore in Tamil Nadu, South India. It is a 2234 bedded tertiary care medical center.

Study subjects:

Patients who underwent intracavitary high dose radiation for cancer cervix.

Scientific title of research scheme: Prospective double blinded randomized cross over study to compare the analgesic effect of Intrathecal hyperbaric bupivacaine with Intrathecal hyperbaric bupivacaine plus ketamine in patients coming for intracavitary high dose radiation (HDR) brachytherapy

Study Type: Prospective double blinded randomized crossover study.

Selection criteria:

Inclusion Criteria: All cases of cancer cervix.

Exclusion Criteria: ASA III and IV

Weight <35 Kg.

Method of randomization: Block randomization of 4 subjects each. In this case six possible

sequences existed (1122, 1212, 1221, 2211, 2121 and 2112) and these sequences or “blocks” were randomly selected till the desired sample size was reached.

Method of allocation concealment: The anaesthetist who performs the block will be informed to which group the patient belongs by the operation theatre staff who is in charge of the randomization list and accordingly the patient will receive spinal bupivacaine with or without ketamine.

Blinding and masking: Except the anaesthetist who does the block, all other staff members are blinded to the drug injected into the subarachnoid space.

Primary outcome: Duration of analgesia of Intrathecal bupivacaine with ketamine.

Secondary Outcome/s: 1. Duration of sensory and motor block.

2. Incidence of side effects like nausea and vomiting, illusions, dreaming, shivering, pruritis, emergence delirium and nystagmus.

Sample size and rationale: The required sample to compare the analgesic duration between the two groups was found to be 20 with a power of 80% with an alpha level significance of 5%.

(This dissertation is based on the pioneer study titled “Effects of Intrathecal Ketamine added to bupivacaine for spinal anaesthesia” **Authors:** Kathirvel,S.; Sadhasivam,S.; Saxena,A. Kannan,T.R.; Ganjoo,P. **Source:** Anaesthesia, Volume 55, Number 9, September 2000, pp. 899-904(6)

Formula:

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 2s^2}{d^2}$$

where,

$$s = \frac{s_1 + s_2}{2}$$

$Z_{1-\alpha/2} = 1.96$ (5% alpha level of significance)

$Z_{1-\beta} = 0.842$ (80% power)

d = difference between the two means

n / 2 in each group

Ref: 1) Design and Analysis of Cross Over Trials by Byron Jones and Michael and Kenward.

**2) Monographers on Statistics and Applied Probability -98 Chapton and Hall
publications pg - 34**

The above studies give the duration of analgesia as one of the monitoring variable which is my primary outcome. Values are mean of 190.7 and 186.3 and SD of 26 and 20.1.

Using the above formula:

$$\begin{aligned} n &= \frac{2 \times (1.96 + 0.842)^2 \times [(26+20.1)/2]^2}{(190.7 + 186.3) / 2} \\ &= 2 \times 7.851204 \times 23.05 \end{aligned}$$

$$\begin{aligned}
 & \frac{\quad}{19.36} \\
 = & 18.69 \\
 n = & \sim 20
 \end{aligned}$$

Therefore each arm will have 10 patients.

Date of first enrolment: June 1st 2008

Estimated duration of trial: 3 months

Methodology:

Patients who receive HDR get 2 fractions of brachytherapy. They will be randomly divided into groups A or B. Group A will receive 2 ml of 0.5% hyperbaric bupivacaine during the 1st fraction and 1.5 ml of 0.5% hyperbaric bupivacaine with 0.5 mg/kg of preservative free ketamine during the 2nd fraction. Group B will receive 1.5 ml of 0.5% hyperbaric bupivacaine with 0.5 mg/kg of preservative free ketamine during the 1st fraction and 2 ml of 0.5%hyperbaric bupivacaine during the 2nd fraction. So each patient will thus be her own

control.

**MODEL
HDR Patients**

Group	1st Fraction	2nd Fraction
A	2ml of 0.5% hyperbaric Bupivacaine	1.5 ml of 0.5% hyperbaric Bupivacaine + 0.5 mg/kg of Ketamine
B	1.5 ml of 0.5% hyperbaric Bupivacaine + 0.5 mg/kg of Ketamine	2 ml of 0.5% hyperbaric Bupivacaine

Patients from groups A and B who are given a combination of 0.5% hyperbaric bupivacaine with ketamine intrathecally will belong to the study group and those who are given 0.5% hyperbaric bupivacaine intrathecally will belong to the control group.

Intervention and Comparator agent

On the previous day the anaesthetist meets the patient, explains about the study and gets an informed consent signed. The patient is kept fasting on the day of the procedure and a premedication of diazepam and metocloperamide is given. Anaesthesia machine and airway equipment are checked according to ASA guidelines. Drugs like atropine, adrenaline, ephedrine, thiopentone and succinylcholine are kept ready.

Patient is then shifted to the operation theatre and monitoring like pulse oximeter, noninvasive blood pressure and electrocardiogram are established. An intravenous access with 20G cannula is attained under aseptic precautions and a 500ml normal saline or ringer lactate solution is connected for preloading during spinal anaesthesia.

A baseline recording of pulse rate, blood pressure and spo2 is noted. Then the

randomization chart is checked and anaesthesia is planned accordingly. Under aseptic precautions lumbar puncture is performed using an appropriate needle at the L₂-L₃ / L₃-L₄ space. The study drug is injected after confirming the free flow of CSF.

The time of onset of sensory and motor block is noted. Sensory blockade is assessed by loss of pin prick sensation in T10-T12 region and motor block is assessed by loss of mobility of foot. Then the patient is shifted to the lithotomy position for the placement of the applicators. During this period vital signs are monitored at 10, 20, 30, 45, 60, 75, 90, 105 and 120 minutes or till the patient is shifted to the recovery room from the operation theatre. Intraoperatively complications like illusions, dreaming, shivering, pruritis, vomiting and nystagmus are checked and treated accordingly.

In the recovery room the nurse monitors the patient till the return of sensory and motor function after which she is shifted to the radiotherapy suite. During this period the patient is monitored by the radiotherapy physicians. The time and the pain score at which the patient asks for an analgesic is noted and a rescue analgesic is given. This period is considered as the duration of analgesia provided by spinal anaesthesia. The data is collected and the groups are compared statistically.

RESULTS

Duration of sensory blockade

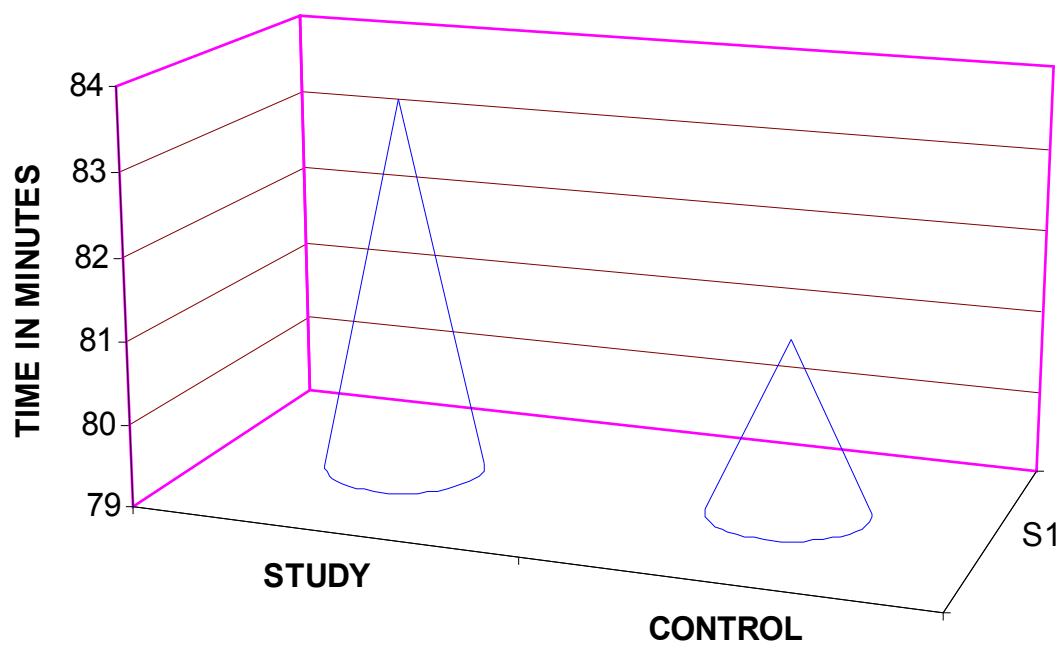


FIGURE - 3

Comparison of duration of sensory blockade between the study group and the control group

	Mean	Std. Deviation
Study	83.55	13.62
Control	81.09	11.90

Mean	SD	t	Df	Significance
2.45455	17.87184	0.644	21	0.526

TABLE - 1

On comparing the duration of sensory block in the study and control groups, the study group had a mean (SD) duration of 83.55(13.62) minutes and control group had 81.09(11.90) minutes. On comparing the groups by the paired't' test it was found to have a p value of 0.526. Hence this study showed that there is no statistically significant difference in the duration of sensory block between the study and control groups.

Duration of motor blockade

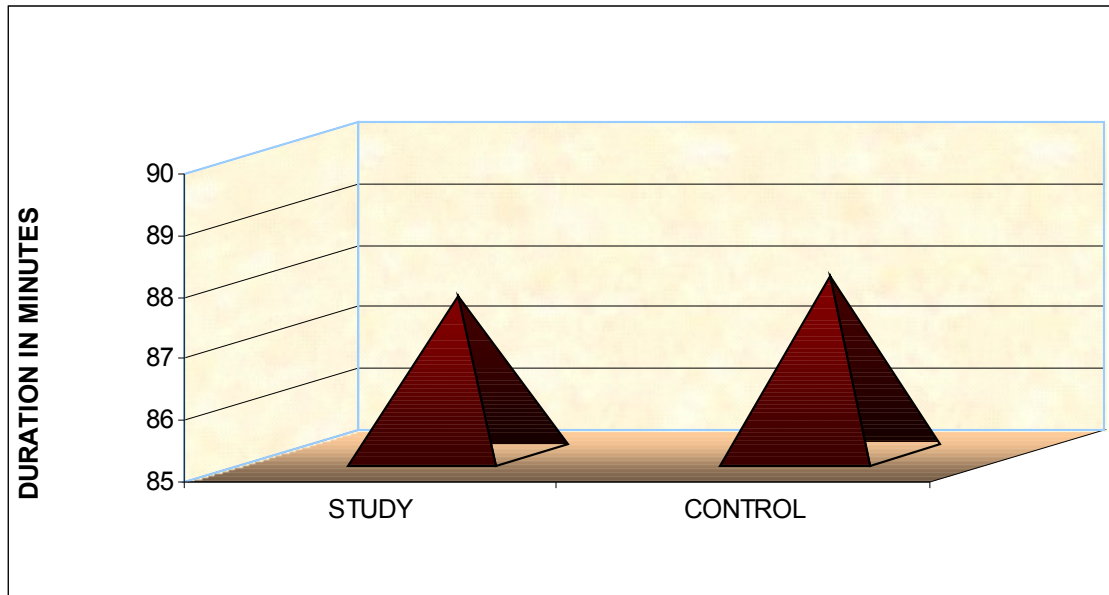


FIGURE - 4

Comparison of duration of motor blockade between the study group and the control group

Study	Mean	Std.Deviation
Control	87.9091	15.15290

Mean	SD	T	Df	Significance
-0.31818	18.73471	-0.080	21	0.937

TABLE - 2

The duration of motor block was compared between the study and control groups. The study group showed a mean (SD) duration of 87.59(14.35) minutes and control group 87.90(15.15) minutes. When compared statistically using the paired't' test, it showed a p value of 0.937 with no significant difference in the duration of motor block.

Duration of analgesia

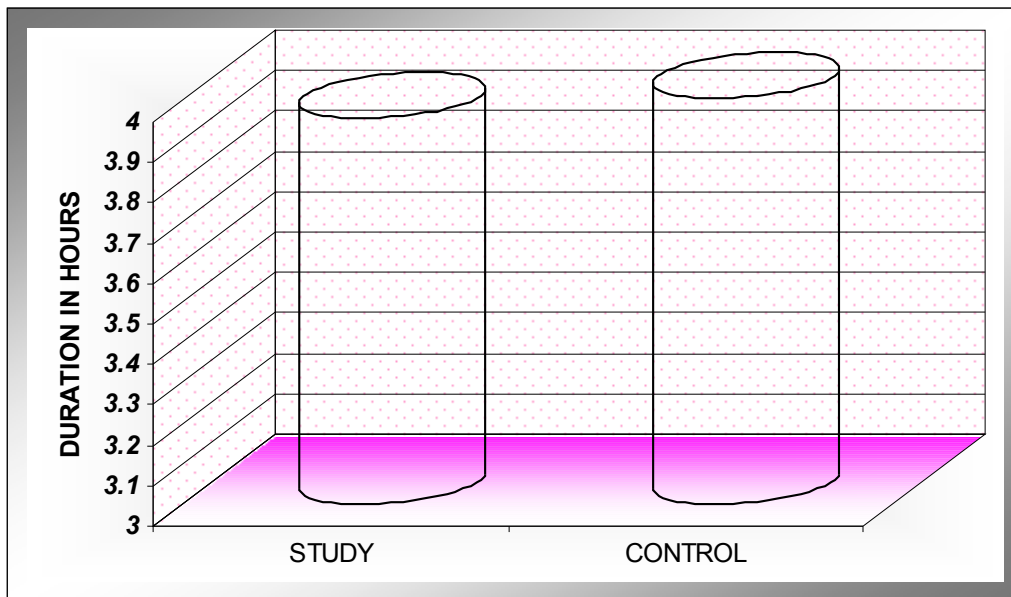


FIGURE - 5

Comparison of duration of analgesia between the study group and the control group

TABLE - 3

Mean	SD	T	Df	Significance
-.05727	1.03100	0.261	21	0.797
Study		3.9518		0.70538
Control		4.0091		0.88158

The study and control groups were compared regarding the duration of analgesia. It was seen that the study group had a mean (SD) duration of 3.95(0.705) hours and control had 4.00(0.88) hours. On comparing these two groups using the paired't' test a p value of 0.797 was obtained , which shows that there is no significant difference between the two groups regarding the duration of analgesia.

The difference in the durations of sensory, motor blockade and analgesia between fractions 1 and 2

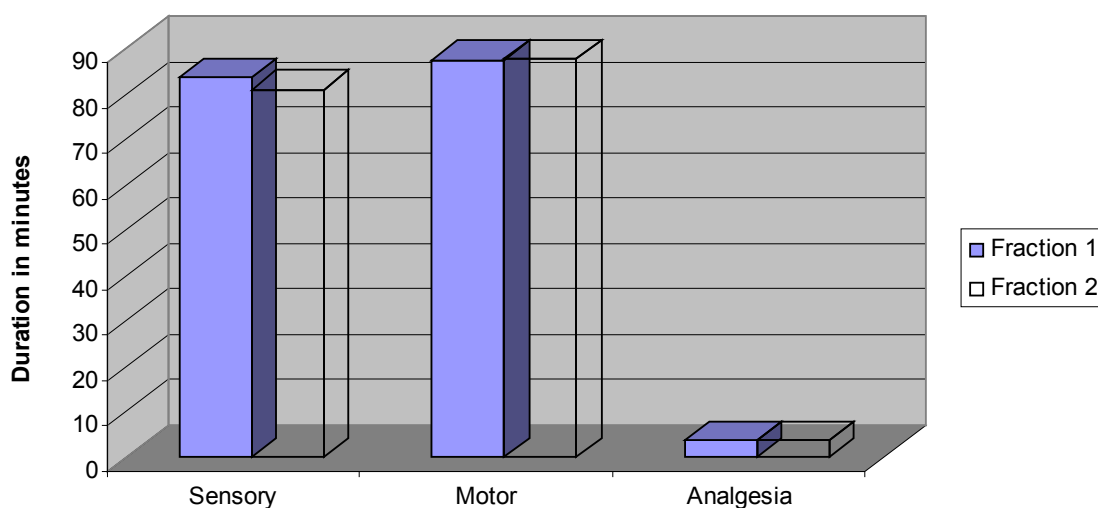


FIGURE - 6

	Mean	SD	T	Df	Significance
Duration of sensory blockade	2.45455	17.87184	0.644	21	0.526
Duration of motor blockade	-0.31818	18.73471	-0.080	21	0.937
Duration of analgesia	-.05727	1.03100	-0.261	21	0.797

The difference in the durations of sensory, motor blockade and analgesia between fractions 1 and 2

TABLE - 4

The patients were compared between the first and the second fraction irrespective of the type of treatment they had received based on the duration of sensory and motor block and analgesia. The p values were 0.526, 0.937, and 0.797 for sensory blockade, motor blockade

and duration of analgesia respectively. It was found to have no statistically significant difference in the duration of sensory and motor block and analgesia irrespective of the number of fraction.

Comparison of systolic BP

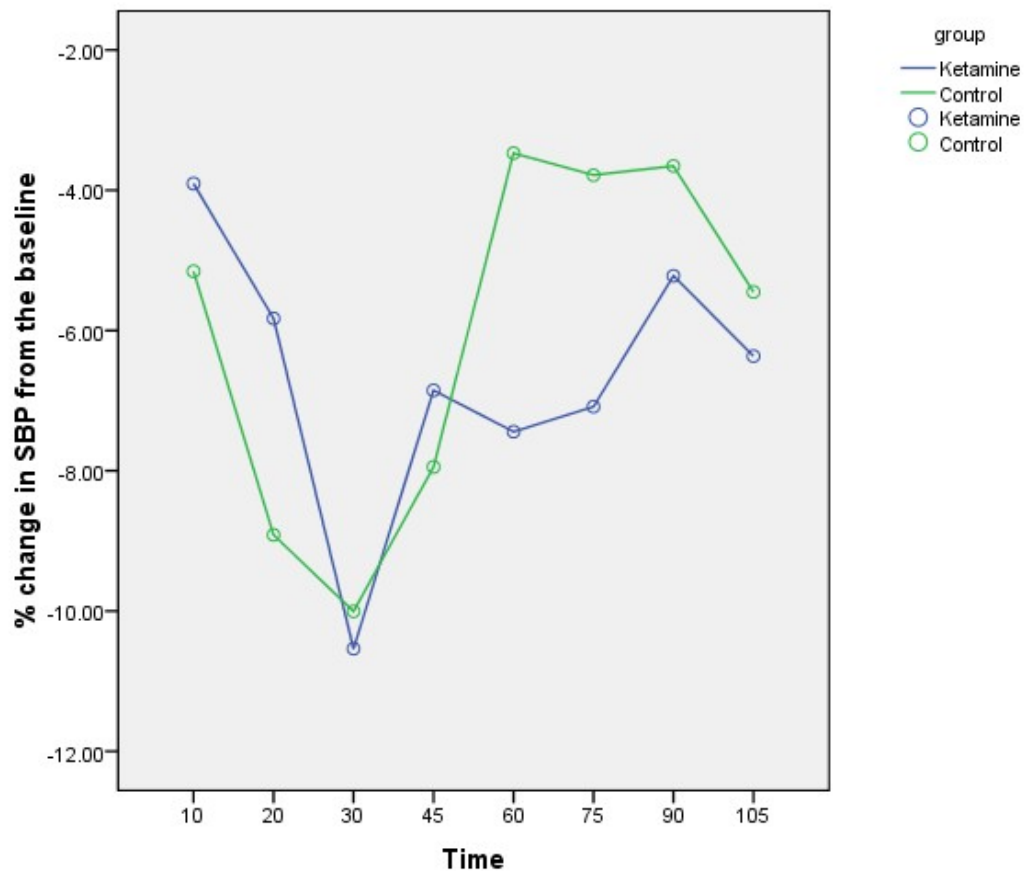


FIGURE - 7

% Change in systolic BP

Change in systolic BP %	10 minutes Mean (SD)	60 minutes Mean (SD)	90minutes Mean(SD)
Study	-3.90 (8.65)	-7.00 (8.24)	-5.22 (6.65)
Control	-5.16 (-5.15)	-3.47 (15.89)	-3.55 (14.80)
t	-0.542	-1.101	-0.492
Deg of freedom	21	20	18
Significance	0.593	0.284	0.629

TABLE - 5

In the study group the fall in systolic BP from the baseline was 3.90%(8.65) at 10 minutes, 7% (8.24) at 60 minutes and 5.22%(6.65) at 90 minutes as compared to the control group where there was a fall of 5.16%(5.15), 3.47%(15.89) and 3.55%(14.80) at 10, 60 and 90 minutes respectively. By using the paired't' test it was found to have p values of 0.593, 0.284 and 0.629 at 10, 60 and 90 minutes, which is not statistically significant.

% Change in Diastolic BP

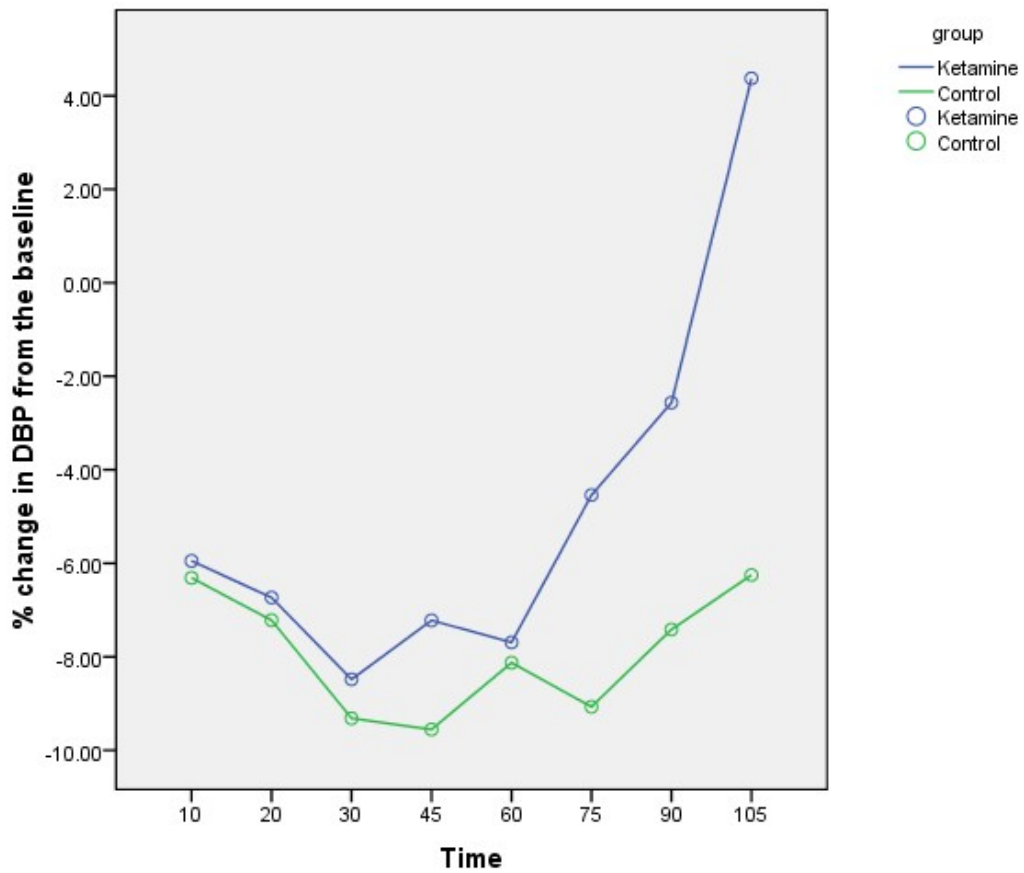


FIGURE - 8

%Change in Diastolic BP

Change in Diastolic BP %	10 minutes Mean (SD)	60 minutes Mean (SD)	90minutes Mean(SD)
Study	-5.95(10.25)	-6.83(16.55)	-2.56(16.09)
Control	-6.31(7.177)	-8.12(8.48)	-7.28(6.75)
Test statistic	0.139	0.322	1.435
Deg of freedom	21	20	18
Significance	0.891	0.751	0.169

TABLE - 6

In the study group the fall in diastolic BP from the baseline was 5.95%(10.25) at 10 minutes, 6.83% (16.55) at 60 minutes and 2.56%(16.09) at 90 minutes as compared to the control group where there was a fall of 6.31%(7.177), 8.12%(8.48) and 7.28%(6.75) at 10, 60 and 90 minutes respectively. By using the paired't' test it was found to have p values of 0.891, 0.751 and 0.169 at 10, 60 and 90 minutes, which is not statistically significant.

% Change in heart rate

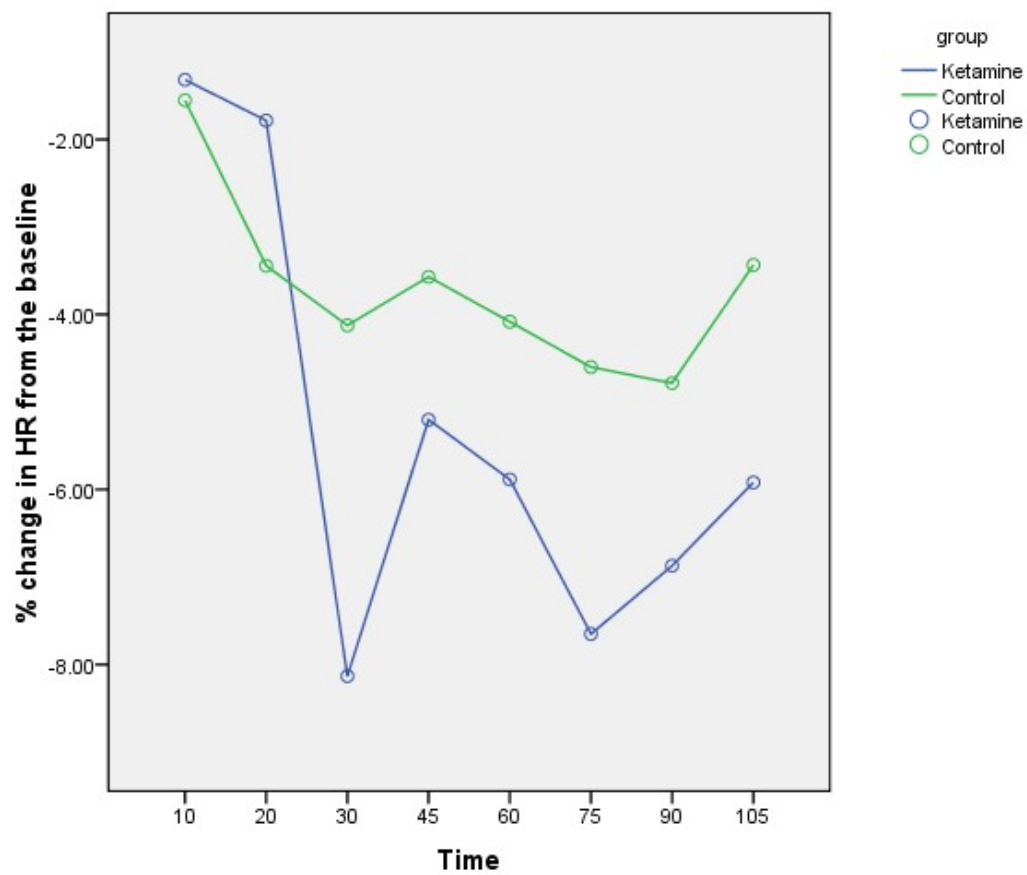


FIGURE - 9

% Change in heart rate

Change in Heart rate %	10 minutes Mean (SD)	60 minutes Mean (SD)	90minutes Mean(SD)
Study	-1.32(5.46)	-6.48 (10.13)	-7.55 (9.83)
Control	-1.55 (6.65)	-4.08 (8.62)	-4.92 (7.34)
t	-0.119	-0.880	-0.947
Deg of freedom	21	20	17
Significance	0.906	0.389	0.357

TABLE - 7

In the study group the fall in heart rate the baseline was 1.32%(5.46) at 10 minutes, 6.48%(10.13) at 60 minutes and 7.55%(9.83) at 90 minutes as compared to the control group where there was a fall of 1.55%(6.65), 4.08% (8.62) and 4.92%(7.34) at 10, 60 and 90 minutes respectively. By using the paired't' test it was found to have p values of 0.906, 0.389 and 0.357 at 10, 60 and 90 minutes, which is not statistically significant.

Comparison of side effects

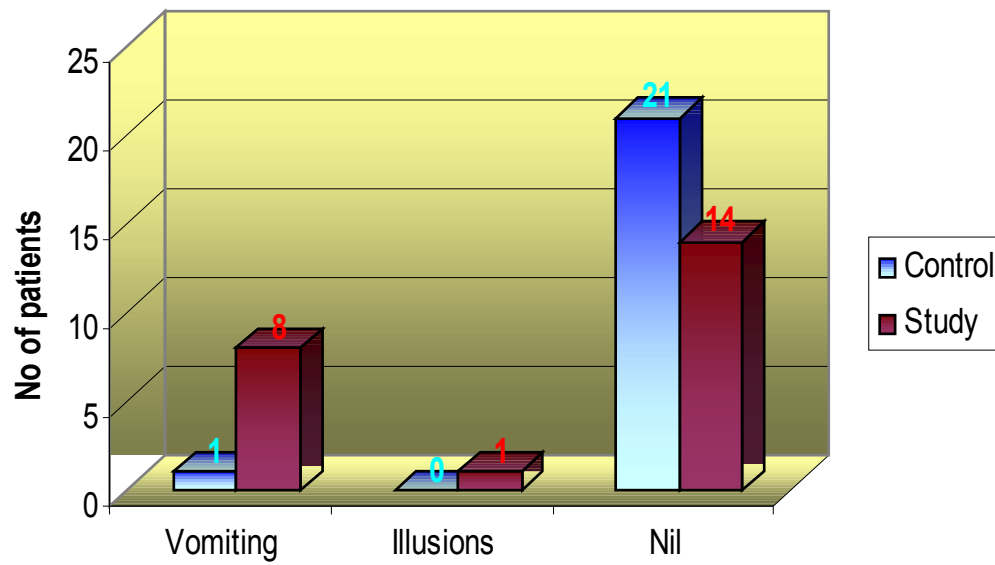


FIGURE - 10

Comparison of side effects

	Control (%)	Study (%)
Vomiting	1 (4.54)	8 (36.36)
Illusions	0	1 (4.54)
Nil	21 (95.45)	14 (63.63)
Total	22 (100)	22 (100)

TABLE - 8

The groups were also compared for the incidence of side effects. The control (bupivacaine only) group had only 1 patient out of 22 (4.5%) but the study (bupivacaine + ketamine) group had 8 patients who vomited (36.36 %). 1 patient from the study group had illusions (4.54%) but none in the control group.

Discussion

The goal of an anaesthetic is to provide ideal surgical conditions and a pain free state extending into the post operative period. Every spinal anaesthetic agent in current practice aims to achieve this goal. Some of the spinal adjuvant drugs in use are morphine, fentanyl, pethidine, clonidine, ketamine and neostigmine. Intrathecal administration of local anaesthetics and narcotics in combination has unrivaled effectiveness in spinal anaesthesia. However opioids' side effects like nausea, vomiting, pruritis, urinary retention and respiratory depression necessitate intervention and delays discharge. Clonidine causes hypotension and sedation while neostigmine causes nausea and vomiting.

Ketamine, a phencyclidine derivative is a well known anaesthetic and analgesic and can also be given intrathecally. It can be used as a sole drug or as an adjuvant with a local anaesthetic and this combination can reduce the total dose of both the drugs and thus their side effects. The intrathecal dose is lower than the intravenous dose which is well known to have various side effects.

Our study compared the duration of analgesia of intrathecal 0.5% hyperbaric bupivacaine with intrathecal 0.5% hyperbaric bupivacaine plus ketamine in patients posted for intracavitary high dose radiation (HDR) brachytherapy. Group A received bupivacaine during the 1st fraction and bupivacaine with ketamine during the 2nd fraction. Group B received bupivacaine with ketamine during the 1st fraction and bupivacaine alone during the 2nd fraction. Thus each patient was her own control. The dose of 0.5% hyperbaric bupivacaine

was 2.0 ml when administered alone and 1.5 ml when combined with 0.5 mg/kg of ketamine. Since these patients have severe pain when the packs are being removed about 4-5 hours later and should be discharged home the same day in a pain free state, oriented and with the absence of side effects like vomiting and respiratory depression, this study was done aiming to achieve this goal.

Duration of analgesia

The primary outcome of our study was to assess the duration of analgesia between the two groups. The mean duration of analgesia in the control group was 4.0091(SD 0.88158) hrs and in the study group it was 3.9518(SD 0.70538) by using the paired 't' test and a p value of 0.797. Though there is a reduction in the duration of analgesia in the study group it is not statistically significant #28) (#27).

The study also shows that there is no statistically significant difference in the duration of analgesia when ketamine was given in the first or the second fraction.

Duration of sensory blockade

The mean duration of sensory block in the study group was 83.55(SD13.623) minutes and in the control group it was 81.09(SD11.90) minutes. By using the paired 't' test a p value of 0.526 was obtained which is not statistically significant. Bhattacharya D et al in his study showed that when bupivacaine is combined with ketamine, it produced a shorter duration of sensory blockade³⁰.

Duration of motor blockade

Like the duration of sensory blockade, the difference in the duration of motor block between the study and control groups was not statistically significant. The mean duration of motor block in the study group was 87.59(SD14.35) minutes and in the control group it was 87.90(SD15.15) minutes with a p value of 0.937.

The effect on blood pressure

Blood pressure was checked at 10, 20, 30, 45, 60, 75, 90, and 105 minutes of the procedure. Both the groups did not show statistically significant difference in the fall in BP as compared to the baseline values. Both the groups had a similar fall of systolic BP to approximately 8-10% and a fall of diastolic BP to approximately 5-7%. This could be attributed to the lithotomy positioning of these patients during the procedure which causes an increase in the venous return to augment the cardiac output. In a study conducted by Miyabe M et al they compared the changes in the fall of systolic BP after spinal in patients positioned in lithotomy position to that who were kept supine. He showed that there was a decreased fall in systolic BP in those who were in the lithotomy position³⁷. None of these patients received vasopressors during the procedure. The ketamine group showed a 4% increase in diastolic BP at the end of the procedure probably due to a sympathomimetic effect.

Heart rate

Bradycardia was noted in both the groups though studies show that ketamine causes

an increase in heart rate. It could be due to loss of sympathetic drive and thereby causing a direct myocardial depressant effect. Bhattacharya D et al in their study showed that 16% of patients in the study group had bradycardia though it was less when compared to 33% of patients in the control group³⁰. Togal T et al had observed bradycardia in their patients²⁷.

Side effects

Of all the patients only one (4.5%) belonging to the study group had delirium. 8 out of 22 (36.36%) patients in the study group and one patient in the control group had vomiting. Kathirvel S et al had an increased incidence of side effects in their patients due to ketamine which included sedation, dizziness, nystagmus, 'strange feelings' and postoperative nausea and vomiting. They had to terminate the study due to these adverse effects³⁶, but Togal T et al did not have any significant difference in the incidence of adverse effects in his study²⁷.

The occurrence of pain

We also checked the mean difference between the pain scores, the time at which the patients complained of pain and the time at which they received the rescue analgesic. Mean (SD) difference of pain score was 1.7273(0.99682) and the time duration was 32.0227(24.54752) between the study and control groups.

CONCLUSION

This study was conducted on patients diagnosed to have carcinoma cervix who underwent intracavitary HDR brachytherapy in two fractions. During the procedure 0.5mg/kg of preservative free ketamine added to 1.5 ml of hyperbaric bupivacaine was compared with 2 ml of 0.5% hyperbaric bupivacaine injected intrathecally and this did not show any significant difference in terms of duration of analgesia, sensory and motor blockade irrespective of the number of fraction. There was an increased incidence of side effects like vomiting and delirium in the study group. Hence this study concludes that ketamine is not an effective spinal adjuvant drug for intracavitary brachytherapy.

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INFORMED CONSENT FORM

Please initial the correct box:

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. []

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. []

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. []

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) []

(v) I agree to take part in the above study. []

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative: _____

Date: ____/____/____

Signatory's Name: _____

Signature of the Investigator: _____

Date: ____/____/____

Intrathecal Ketamine with Bupivacaine study for intracavitary HDR Brachytherapy patients.

Information sheet

So far in CMC, applicators for radiotherapy have been inserted under spinal anesthesia using the drug bupivacaine. This keeps the patient pain free for 2-3 hours. However many patients complain of pain for 4-5 hours later when the applicators and vaginal packs are removed. The addition of a drug, like ketamine, which could act additively or synergistically, may increase the 'pain free period'. In order to investigate this we plan to study the duration of analgesia (pain free period) with and without the addition of ketamine to the spinal drug bupivacaine. You have to tell us whether you are comfortable or not and whether you have pain or not after the procedure. If you do have pain we would like you to inform us when it occurs and how severe it is. The measurement or description of severity will be explained to you in detail before the procedure.

Are any side effects involved?

The drug ketamine which we are adding is a safe drug which has been used in other patients before. Rarely, it is known to cause raised blood pressure and increased heart rate and increased salivation. It can also occasionally cause confusion and strange feelings. This usually occurs only with larger doses, but the amount of drug we are giving is well below the amount which can cause the above side effects.

What benefits do you get by participating in the study?

You ought to get the benefits of better pain relief and if the study shows that by doing so it provides good analgesia then we plan to add the drug ketamine to all the patients coming for the procedure. Thus you will help many more patients by participating in the study.

Any appropriate alternatives?

We can add other drugs like fentanyl and morphine but they have side effects such breathing problems, vomiting, itching and urinary problems. This can occur soon after the procedure or even much later. As you will be discharged the same day (HDR), these drugs are more risky. So we have planned to add ketamine which has fewer and milder side effects.

What about the secrecy of the information?

Your personal information will not be disclosed to anyone other than the medical personnel looking after you. It will not appear anywhere in print. Your identity will be known only to the anesthetist and the radiation oncologists and others involved in the study.

How will you will be selected or the study?

For (HDR) patients you will have to undergo radiations two to three times, we will be considering your two radiations for study, so you will be getting the spinal once with and once without ketamine. The ketamine may be given either the first time or second time.

What do you have to do on participating in the study?

In this study we will be monitoring your pain status. So we have a scale which shows numbers from 0 to 10, with 0 meaning no pain and progressively increasing pain till 10 which means intolerable pain. When you complain of pain you will be asked to quantify your pain between "0 to 10" and note the time of start of pain and time u get the rescue analgesic which should be written in a paper provided.

Participation in this study?

The participation in this study is completely voluntary.

Intrathecal Ketamine with Bupivacaine study for Intracavitary HDR Brachytherapy

SL No : Date :
 Name : Hospital No :
 Age : Yrs Height : cms Weight : kgs
 Diagnosis :
 Premedication : Diazepam 5mg and Metaclopramide 10mg 1hr prior surgery

Ist fraction	
IInd fraction	

Spinal Anesthesia

Technique as preferred by Anesthetist.

O2 through Hudson mask 4lts/min .

IV fluids NS as required.

Exclusion criteria : **1]** ASA III / IV **2]** Wt < 35 kgs **3]** Contraindication for spinal block

Inclusion criteria : All other than Exclusion criteria

Intra-operative Events

mins	0	10	20	30	45	60	75	90	105	120
HR										
BP										
Spo2										

Side effects : Illusions / Dreaming / Shivering / Pruritis / Vomiting / Sedation / Nystagmus

	Time
Time of spinal anesthesia	
Onset of sensory block	
Onset of motor block	
Return of sensation	
Return of foot movements	

Rescue drug given

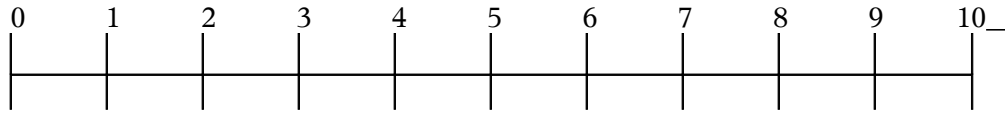
Time	Drug

Onset of sensory block is checked for pin prick at T10-12 level. Onset of motor block is tested by checking for absence of movement of foot.

Amount of iv fluids given till u shift the pt out of OR : _____ml

PAIN ASSESSMENT

VISUAL ANALOUGE SCALE



No pain

Worst Pain

Post-operative

Time of first report of pain : _____ am/pm Pain score : _____

Rescue Drug given

Time							
Pain score							
Drug							

Side effects : Illusions / Dreaming / Shivering / Pruritis / Vomiting / Sedation / Nystagmus

Rescue drugs :

- Vomiting -- Inj Ondansetron 4mg IV stat
- Hypotension -- Inj Ephedrine 5mg IV stat, if SBP < 90mmHg or fall > 20% of baseline value. To be repeated if necessary
- Pain -- Inj Tramadol 100 mg iv stat.

Master chart : please look into the the xl sheet by name **justinakmastersheet**. In the same cd.